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Vinylidene Homologation of Boronic Esters and its Application to the Synthesis of the Proposed Structure of Machillene

James M. Fordham,[a] Matthew N. Grayson*[b] and Varinder K. Aggarwal*[a]

Abstract: Alkenyl boronic esters are important reagents in organic synthesis. Herein, we report that these valuable products can be accessed by the homologation of boronic esters with lithiated epoxysilanes. Aliphatic and electron-rich aromatic boronic esters provided vinylidene boronic esters in moderate to high yields, while electron-deficient aromatic and vinyl boronic esters were found to give the corresponding vinyl silane products. Through DFT calculations, this divergence in mechanistic pathway has been rationalized by considering the stabilization of negative charge in the C-Si and C-B bond breaking transition states. This vinylidene homologation was used in a short six step stereoselective synthesis of the proposed structure of machillene, however, synthetic and reported data were found to be inconsistent.

Vinyl boronic esters are versatile intermediates in organic chemistry, participating in a range of transformations including cross-coupling,[1] oxidation,[2] homologation[3] and many others.[4] Due to their synthetic utility, new methodologies that expand the range of accessible vinyl boronic esters are highly desirable, especially those that enable the introduction of sp^3-rich motifs. Many precursors have been used to prepare vinyl boronic esters including alkynes,[5] vinyl halides,[6] alkenes,[7] carboxylic acids,[8] aldehydes,[9] ketones[10] and, recently, boronic esters themselves. Through modification of their conjunctive cross-coupling methodology,[11] Morken and co-workers were able to achieve the vinylidenation of organoboronic esters **1** to prepare a range of 1,1-disubstituted vinyl boronic esters **3** (Figure **1**).[12] As sp^3-rich organoboronic esters are readily available,[13-15] vinylidene homologations have the potential to greatly expand the range of available vinyl boronic esters. Furthermore, we envisaged a process wherein iterative homologation of a boronic ester could be interrupted by a vinylidenation protocol to create more diverse polyketide-type structures.[16]

Inspired by our previous work on the reaction of lithiated epoxides with boronic esters,[17] we set out to exploit the reaction of lithiated epoxysilane **4** with boronic esters **1** in a novel vinylidene homologation (Figure **1**). We postulated that after formation of a boron-ate complex, 1,2-metallate rearrangement would occur to give β-alkoxy-α-silyl boronic ester intermediate **5**, which could undergo a Peterson-type elimination[18] to give vinyl boronic ester **3**. If successful, this method would serve as a transition-metal free alternative to the procedure of Morken. Based on previous reports,[19] we anticipated that the desired Peterson elimination pathway would be favoured over the alternative boron-Wittig reaction (forming vinyl silane **6**),[20] although the mechanistic rationale for this outcome remained unclear.

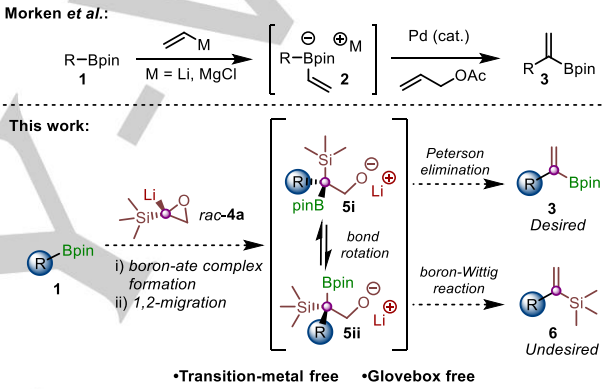

Figure 1. Vinylidene homologation of boronic esters.

Encouraged by this precedent, we reacted phenethyl boronic ester **1a** with lithiated epoxysilane **4a** (Table 1).[21] After stirring at 40 °C for 1 h, ^{11}B NMR analysis of the reaction mixture indicated that full 1,2-migration had occurred and, after chromatographic purification, vinyl boronic ester **3a** was obtained as the exclusive product in 77% yield (see S.I. for optimisation). The methodology was found to be compatible with more sterically hindered secondary and tertiary boronic esters (products **3b** and **3c**), although the latter case required higher stoichiometry of **4** for optimum yield. Boronic esters containing base and nucleophile-sensitive groups were also employed and the corresponding homologated products **3d** and **3e** were obtained in 49% and 38% yield, respectively. We were eager to investigate more elaborate and pharmaceutically relevant boronic esters. Thus, cyclobutyl and azetidinyl substrates were subjected to the vinylidenation reaction and gave the corresponding products **3f** and **3g** in 72% and 55% yield, respectively, the former being obtained with complete diastereospecificity (d.s.). The sensitive vinyl cyclopropyl boronic ester **3h** was isolated in 51% yield (75% NMR yield). Sterically hindered menthyl and cholesteryl-derived boronic esters gave vinylidene products **3i** and **3j** in lower yield (32% and 46%, respectively) with a small amount of over-homologation apparent. A polyketide-type substrate was also subjected to the reaction conditions, giving the desired product **3k**

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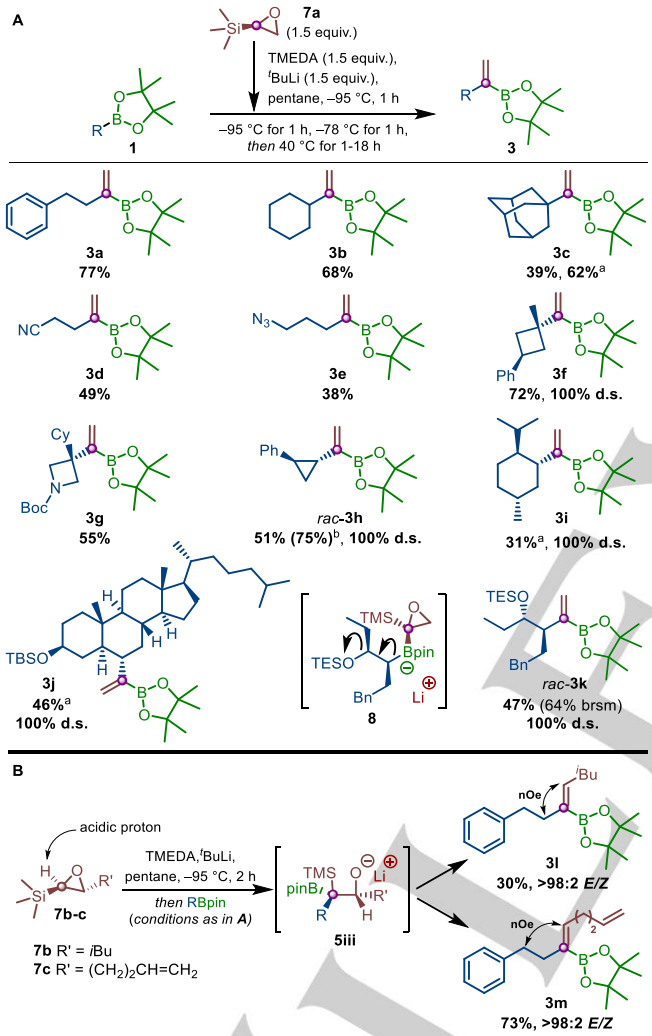
in 47% yield. This substrate is notable considering the potential for β-elimination via intermediate **8**, which was not observed under our reaction conditions.[22] As lithiated epoxysilanes are configurationally stable at low temperature,[21] we expected that a *trans*-substituted epoxysilane would furnish the trisubstituted (*E*)-olefin with high selectivity *via* intermediate **5iii** (Table 1B). Indeed, epoxysilanes **7b** and **7c**,[23] gave the corresponding products **3l** and **3m** in 30% and 73% yield respectively and as a single isomer.

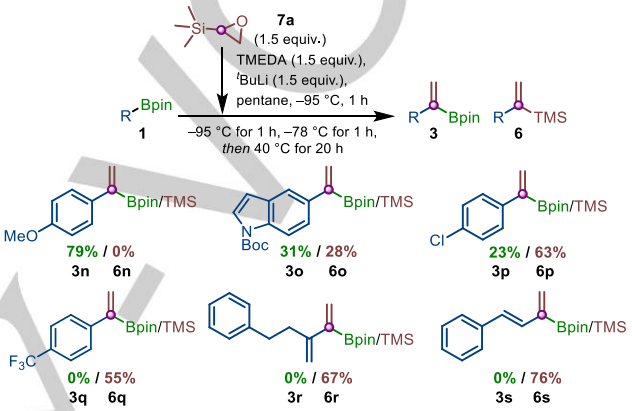
Table 1. Vinylidene homologation of aliphatic boronic esters.



Yields are of isolated products. Diastereomeric ratios were determined by ^{1}H NMR analysis of the isolated products. [a] Reaction performed using 2.5–3.0 equiv of lithiated epoxide, see SI for details. [b] Yield in parentheses was determined by ^{1}H NMR using CH_2Br_2 as an internal standard. Cy: cyclohexyl; TMS = trimethylsilyl; TES: triethylsilyl; TBS: *tert*-butyldimethylsilyl; ^{i}Bu: isobutyl; nOe = nuclear Overhauser effect.

The reaction conditions were then applied to sp^2-hybridised boronic esters, which required longer reaction times due to the reduced migratory aptitude of vinyl and aryl groups (Table 2).[24] While the electron rich, *p*-methoxyphenyl boronic ester **1n** gave the vinyl boron product **3n** in 79% yield, indolyl boronic ester **1o** gave a mixture of vinyl boronic ester **3o** and vinyl silane **6o** in 31% and 28% yield, respectively. This divergence in elimination pathway was even more pronounced for electron deficient aryl systems. For example, *p*-chlorophenyl boronic ester **1p** gave vinyl silane **6p** as the major product and, in the most extreme case, *p*-trifluoromethylphenyl boronic ester **1q** gave exclusively vinyl silane **6q** in 55% yield. Vinyl boronic ester starting materials also gave vinyl silane products **6r** and **6s** instead of the corresponding vinyl boronic esters.

Table 2. Vinylidene homologation of sp^2-hybridised boronic esters.



DFT calculations were performed to better understand the factors that determined the outcome of the elimination pathway. All calculations were performed with Gaussian 16[25] at the B3LYP-D3(BJ)/6-311G(d,p)−IEFPCM(n-pentane)//B3LYP/6-31G(d) level of theory (see S.I. for computational details). Previous computational studies of organic reactions with similar methods provided results in accord with experiment.[26-28]

The thermodynamically favoured product was calculated to be the vinyl silane by over 3 kcal mol^{-1} for sp^3- and sp^2-hybridised boronic ester substituents (Table S12). To gain insight into the origins of product selectivity, C-Si and C-B bond breaking transition states (TSs) **9a** and **9b** were located and their relative energies determined (Table 3). For aliphatic substrates, the R group was modelled as a methyl substituent to reduce the number of possible conformations. In this case, the C-Si bond breaking TS was favoured by over 9 kcal mol^{-1} relative to the C-B bond breaking TS (entry 1), indicating a strong preference for the vinyl boronic ester product, as observed. For substrate **1n**, with a *p*-methoxyphenyl substituent, the C-Si bond breaking TS was favoured by 1.2 kcal mol^{-1} (entry 2), whilst for indolyl substrate **1o** the TSs were separated by only 0.2 kcal mol^{-1} (entry 3). On the other hand, for *p*-trifluoromethylphenyl substrate **1q**, the C-B bond breaking TS was favoured by 1.4 kcal mol^{-1} (entry 4), and in the case of styrenyl boronic ester **1s**, this increased to 5.6 kcal mol^{-1} (entry 5). These calculated TS energies are in good agreement with the experimentally observed product distributions. The results can be understood by considering how the developing negative charge on carbon is stabilized in the TS of the C-Si and C-B bond breaking step.[29-30] Evidently, the charge is better stabilized by the electron deficient boron than by silicon, leading to the vinyl boronic ester products. Indeed, our calculations show

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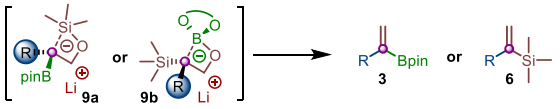
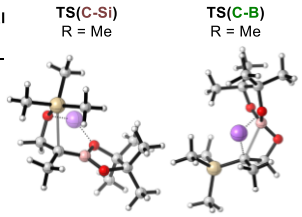
that boron is better able to stabilize negative charge than silicon by 9.1 kcal mol^{-1} (Table S10). However, for substrates that already bear anion stabilizing groups, elimination takes place preferentially at the more Lewis acidic boron atom, leading to the vinyl silane products.

Table 3. Comparison of C-Si and C-B bond breaking TSs for vinylidenation of MeBpin (**1t**), **1n**, **1o**, **1q** and **1r**. B3LYP-D3(BJ)/6-311G(d,p)−IEFPCM(n-pentane)//B3LYP/6-31G(d)



Entry	R =	ΔΔ$G^{‡}$ (kcal/mol) C–Si / C–B	Experimental C–Si : C–B
1	Me	0 / 9.2	100 : 0[a]
2	*p*-MeOC_6H_4	0 / 1.2	100 : 0
3	indolyl	0.2 / 0	53 : 47
4	*p*-$CF_3C_6H_4$	1.4 / 0	0 : 100
5	styrenyl	5.6 / 0	0 : 100



[a] Aliphatic boronic esters gave exclusively the vinyl boronic ester products. The C-Si and C-B bond breaking TSs for **9t** (R = Me) are shown.

Finally, we sought to apply our chemistry in natural product synthesis. We were attracted to machillene (**10a**), a bis-steryl epoxide isolated from the stem wood of *machilus zuihoensis* (Figure 2A), because it showed significant anticancer activity.[31] Furthermore, the relative configuration of the molecule remained unknown, apart from the epoxide groups, which were assigned as *trans* from analysis of the coupling constants (J = 2.4 Hz). From the reported data, it was apparent that the molecule was neither C_2-symmetric (^{1}H and ^{13}C NMR data) nor meso ([α]$^{23}_D$ = + 22.2°), allowing us to eliminate six of the possible eight diastereoisomers. Based on chemical shift differences between the methylene protons, Breit assigned the methyl substituents of **10a** as having an *anti*-relationship (Δδ = 0 ppm observed, Δδ > 0.5 ppm for the *syn* isomer).[32] Compound **10b** was therefore identified as the most likely structure of the natural product and we set out to confirm its structure through synthesis. Our retrosynthetic analysis began with sequential epoxidation reactions from tetraene **11**. We envisaged the carbon skeleton would be constructed through a bidirectional approach from methylene diboron (**14**), comprised of homologations with lithiated TIB ester **13**[33] and lithiated epoxysilane **4a**, followed by a Pd-catalysed allylic cross-coupling reaction. If successful, the route would give access to machillene in just 6 steps from commercially available diboron **14**, and without the need for protecting groups.

Our synthesis began with homologation of **14** with lithiated species **13**, giving bis-boronic ester **15** in 83% yield, and as a single diastereoisomer (Figure 2B). The vinylidene homologation reaction gave bis-vinyl boronic ester **16** in 58% yield together with mono-vinyl boronic ester **17** in 9% yield. The next step involved a Pd-catalysed allylic cross-coupling reaction between **16** and allylic acetate **12**. To our knowledge there is just a single report that describes the coupling of a vinyl boronic ester with an allylic acetate, however these conditions ($PdCl_2$/TFP, KF, MeOH, rt) led to a low yield of **11** with significant decomposition.[34] We therefore investigated alternative conditions and found that using Pd(dppf)Cl_2 and K_3PO_4 in dioxane/water gave tetraene **11** in 69% yield together with migratory insertion product **18** (see S.I. for a mechanistic proposal).[35]

The end game was particularly challenging and required (i) selective reaction of the styrene over the 1,1-disubstituted alkene (ii) reagent-controlled diastereoselective epoxidation (iii) isolation of the monoepoxide from the statistical mixture of SM, mono- and di-epoxides that would be expected. Following this reaction, a second epoxidation of the monoepoxide with the enantiomeric epoxidation reagent should occur on the remaining styrene with the correct stereochemical outcome. Our initial attempts were based around the Shi epoxidation but no conversion to the desired mono-epoxide **19** was observed and instead starting material was recovered.[36] We then explored the Sharpless dihydroxylation,[37] a reaction where styrenes are known to be more reactive than 1,1-disubstituted alkenes.[38] To our delight, the reaction provided diol **20** in 34% yield, with excellent diastereoselectivity, and with no evidence of reaction at the 1,1-disubstituted double bond. Starting material **11** was recovered (37%) and the C_2-symmetric bis-dihydroxylation product **21** was obtained in 13% yield. After a second dihydroxylation reaction using the pseudo-enantiomeric reagent and subsequent ring-closing,[39] the target molecule was obtained.

Unfortunately, upon comparison of the reported NMR data with that of our synthetic sample, significant differences were observed. The considerable deviations (see S.I. for tabulated data) led us to the conclusion that the issue was not related to stereochemistry, but instead was likely due to a misassignment in the connectivity of the molecule. Further efforts to elucidate the structure of machillene are currently underway in our laboratory using a combination of computational and synthetic methods.

In summary, we have developed a new protocol for the vinylidene homologation of boronic esters that provides access to a diverse range of 1,1-disubstituted and trisubstituted vinyl boronic esters. Computational studies have revealed that both the Peterson and boron-Wittig pathways are feasible but the Peterson pathway is favoured because boron can better stabilize the negative charge developing on the α-carbon in the transition-state of the elimination step. The methodology was used in a short, stereoselective synthesis of machillene but, upon comparing the reported and synthetic NMR data, it was clear that the structure of the natural product had been mis-assigned.

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Keywords: organoboron • homologation • stereospecific • natural product • vinyl boronic ester

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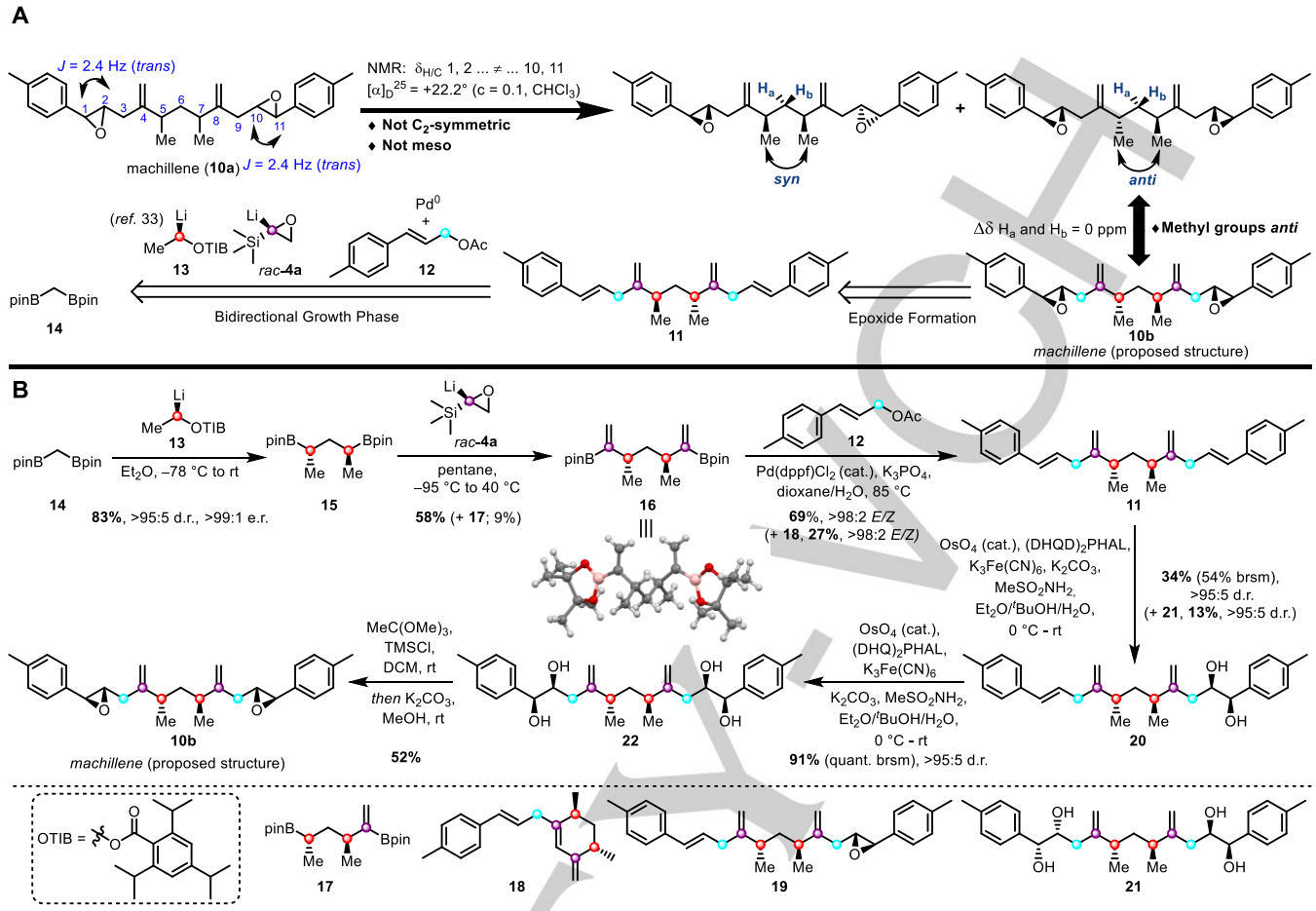

Figure 2. A) Structure determination and retrosynthesis of machillene. B) Total synthesis of the proposed structure of machillene.

[1] a) P. Y. S. Lam, G. Vincent, D. Bonne, C. G. Clark, *Tetrahedron Lett.* **2003**, *44*, 4927–4931; b) R. E. Shade, A. M. Hyde, J. C. Olsen, C. A. Merlic, *J. Am. Chem. Soc.* **2010**, *132*, 1202-1203; c) G. Evano, N. Blanchard M. Toumi, *Chem. Rev.* **2008**, *108*, 3054-3131; d) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457-2483; e) N. Miyaura, M. Satoh, A. Suzuki, *Tetrahedron Lett.* **1986**, *27*, 3745-3748.

[2] a) T. Ohmura, H. Taniguchi, Y. Kondo, M. Suginome, *J. Am. Chem. Soc.* **2007**, *129*, 3518-3519; b) K. Yeung, F. J. T. Talbot, G. P. Howell, A. P. Pulis, D. J. Procter, *ACS Catal.* **2019**, *9*, 1655-1661.

[3] a) J. L-Y. Chen, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2014**, *53*, 10992-10996. *Angew. Chem.* **2014**, *126*, 11172-11176; b) M. J. Hesse, S. Essafi, C. G. Watson, J. N. Harvey, D. Hirst, C. L. Willis, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2014**, *53*, 6145-6149. *Angew. Chem.* **2014**, *126*, 6259-6263; c) D. S. Matteson, D. Majumdar, *J. Am. Chem. Soc.* **1980**, *102*, 7590-7591.

[4] a) D. S. Matteson, *Tetrahedron* **1989**, *45*, 1859-1885; b) G. Zweifel, H. Arzoumanian, C. C. Whitney, *J. Am. Chem. Soc.* **1967**, *89*, 3652-3653; c) M. Kischkewitz, K. OkamotoC. Mück-Lichtenfeld, A. Studer *Science*, **2017**, *355*, 936-938; d) M. Silvi, C. Sandford, V. K. Aggarwal, *J. Am. Chem. Soc*. **2017**, *139*, 5736-5739; e) A. A. Szymaniak, C. Zhang, J. R. Coombs, J. P. Morken, *ACS Catal*. **2018**, *8*, 2897-2901; f) W. J. Moran, J. P. Morken, *Org. Lett.* **2006**, *8*, 2413-2415; g) J. Carreras, A. Caballero, P. J. Pérez, *Chem. Asian. J.* **2019**, *14*, 329-343.

[5] a) H. C. Brown, S. K. Guptalz, *J. Am. Chem. Soc.* **1972**, *94*, 4370-4371; b) C. E. Tucker, J. Davidson, P. Knochel, *J. Org. Chem.* **1992**, *57*, 3482-3485; c) K. Wen, J. Chen, F. Gao, P. S. Bhadury, E. Fanb, Z. Sun, *Org. Biomol. Chem.* **2013**, *11*, 6350-6356; d) I. Beletskaya, A. Pelter, *Tetrahedron*, **1997**, *53*, 4957-5026; e) H. Yoshida, *ACS Catal.* **2016**, *6*, 1799-1811; f) T. Ohmura, Y. Yamamoto, N. Miyaura, *J. Am. Chem. Soc.* **2000**, *122*, 4990-4991.

[6] J. Takagi, K. Takahashi, T. Ishiyama, N. Miyaura, *J. Am. Chem. Soc.* **2002**, *124*, 8001-8006.

[7] a) C. Morrill, R. J. Grubbs, *J. Org. Chem.* **2003**, *68*, 6031-6034; b) R. Hemelaere, F. Carreaux, B. Carboni, *J. Org. Chem.* **2013**, *78*, 6786–6792; c) E. T. Kiesewetter, R. V. O'Brien, E. C. Yu, S. J. Meek, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2013**, *135*, 6026-6029.

[8] H. Cao, H. Jiang, H. Feng, J. M. C. Kwan, X. Liu, J. Wu, *J. Am. Chem. Soc.* **2018**, *140*, 16360-16367.

[9] a) Y. Kishi, *et al. J. Am. Chem. Soc.* **1989**, *111*, 7525-7530; b) J. R. Coombs, L. Zhang, J. P. Morken, *Org. Lett.* **2015**, *17*, 1708-1711.

[10] a) S. Namirembe, C. P. Gao, R. P. Wexler, J. P. Morken, *Org. Lett.* **2019**, *21*, 4392-4394; b) S. H. Cho, J. F. Hartwig, *Chem. Sci.* **2014**, *5*, 694-698.

[11] L. Zhang, G. J. Lovinger, E. K. Edelstein, A. A. Szymaniak, M. P. Chierchia, J. P. Morken, *Science* **2016**, *351*, 70-74.

[12] M. D. Aparece, C. Gao, G. L. Lovinger, J. P. Morken, *Angew. Chem. Int. Ed.* **2019**, *58*, 592-595. *Angew. Chem.* **2019**, *131*, 602-605.

[13] a) M. Burns, S. Essafi, J. R. Bame, S. P. Bull, M. P. Webster, S. Balieu, J. W. Dale, C. P. Butts, J. N. Harvey, V. K. Aggarwal, *Nature*, **2014**, *513*, 183-188; b) G. Casoni, M. Kucukdisli, J. M. Fordham, M. Burns, E. L. Myers, V. K. Aggarwal, *J. Am. Chem. Soc.* **2017**, *139*, 11877-11886; c) D. S. Matteson, *Acc. Chem. Res.* **1988**, *21*, 294-300;

[14] a) G. Zweifel, N. R. Ayyangar, T. Munekata, H. C. Brown, *J. Am. Chem. Soc.* **1964**, *86*, 1076-1079; b) J. R. Smith, B. S. L. Collins, M. J. Hesse, M. A. Graham, E. L. Myers, V. K. Aggarwal, *J. Am. Chem. Soc.* **2017**, *139*, 9148-9151;

[15] a) C. Li, J. Wang, L. M. Barton, S. Yu, M. Tian, D. S. Peters, M. Kumar, A. W. Yu, K. A. Johnson, A. K. Chatterjee, M. Yan, P. S. Baran, *Science* **2017**, *356*, eaam7355; b) J. Wu, L. He, A. Noble, V. K. Aggarwal, *J. Am. Chem. Soc.* **2018**, *140*, 10700-10704; c) F. W. Friese, A. Studer, *Angew. Chem. Int. Ed.* **2019**, *58*, 9561-9564. *Angew. Chem.* **2019**, *131*, 9661-9665.

[16] T. Bootwicha, J. M. Feilner, E. L. Myers, V. K. Aggarwal, *Nat. Chem.* **2017**, *9*, 896-902.

[17] a) E. Vedrenne, O. A. Wallner, M. Vitale, F. Schmidt, V. K. Aggarwal, *Org. Lett.* **2009**, *11*, 165-168; b) A. P. Pulis, V. K. Aggarwal, *J. Am. Chem. Soc.* **2012**, *134*, 7570-7574; For related work, see: c) K. Bojaryn, S. Fritsch, C. Hirschhaüser, *Org. Lett.* **2019**, *21*, 2218-2222.

[18] a) T. Chan, *Acc. Chem. Res.* **1977**, *10*, 442-448; b) L. F. van Staden, D. Gravestock, D. J. Ager, *Chem. Soc. Rev.* **2002**, *31*, 195-200.

[19] a) D. S. Matteson, D. Majumdar, *Organometallics* **1983**, *2*, 230-236; b) M. Shimizu, T. Fujimoto, H. Minezaki, T. Hata, T. Hiyama, *J. Am. Chem. Soc.* **2001**, *123*, 6947-6948.

[20] a) A. Pelter, D. Buss, E. Colclough, B. Singaraman, *Tetrahedron* **1993**, *49*, 7077-7103; b) T. Kawashima, N. Yamashita, R. Okazaki, *J. Am. Chem. Soc.* **1995**, *117*, 6142-6143.

[21] J. J. Eisch, J. E. Galle, *J. Organomet. Chem.* **1988**, *341*, 293-313.

[22] A. Fawcett, D. Nitsch, M. Ali, J. M. Bateman, E. L. Myers, V. K. Aggarwal, *Angew. Chem. Int. Ed.* **2016**, *55*, 14663-14667. *Angew, Chem.* **2016**, *128*, 14883-14887.

[23] Epoxysilanes **7b/c** were prepared using the procedure described in the following paper: D.M. Hodgson, N. J. Reynolds, S. J. Coote, *Tetrahedron Lett.* **2002**, *43*, 7897-7897.

[24] a) R. Robiette, G. Y. Fang, J. N. Harvey, V. K. Aggarwal, *Chem. Commun*. **2006**, 741-743; b) R. Larouche-Gauthier, C. J. Fletcher, I. Couto, V. K. Aggarwal, *Chem. Commun.* **2011**, *47*, 12592-12594.

[25] M. J. Frisch, et al. Gaussian 16; Gaussian, Inc., Wallingford, CT, 2016.

[26] L. Simón, J. M. Goodman, *Org. Biomol. Chem.* **2011**, *9*, 689–700.

[27] Y. H. Lam, M. N. Grayson, M. C.Holland, A. Simon, K. N. Houk, *Acc. Chem. Res.* **2016**, *49*, 750–762.

[28] B. N. Falcone, M. N. Grayson, J. B. Rodriguez, *J. Org. Chem.* **2018**, *83*, 14683–14687.

[29] M. B. Gillies, J. E. Tønder, D. Tanner, P. O. Norrby, *J. Org. Chem.* **2002**, *67*, 7378–7388.

[30] R. Robiette, J. Richardson, V. K. Aggarwal, J. N. Harvey, *J. Am. Chem. Soc.* **2006**, *128*, 2394–2409.

[31] M. Cheng, I. Tsai, S. Lee, B. Jayaprakasam, I. Chen, *Phytochemistry* **2005**, *66*, 1180-1185.

[32] Y. Schmidt, K. Lehr, L. Colas, B. Breit, *Chem. Eur. J.* **2012**, *18*, 7071-7081.

[33] D. J. Blair, D. Tanini, J. M. Bateman, H. K. Scott, E. L. Myers, V. K. Aggarwal, *Chem. Sci.* **2017**, *8*, 2898-2903.

[34] G. Ortar, *Tetrahedron* **2003**, *44*, 4311-4314.

[35] F. Krätzschmar, M. Kaßel, D. Delony, A. Breder, *Chem. Eur. J.* **2015**, *21*, 7030-7034.

[36] O. A. Wong, Y. Shi, *Chem. Rev.* **2008**, *108*, 3958-3987.

[37] H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483-2547.

[38] W. Zhang, R. G. Carter, *Org. Lett.* **2005**, *7*, 4209-4212.

[39] H. C. Kolb, K. B. Sharpless, *Tetrahedron* **1992**, *48*, 10515-10530.

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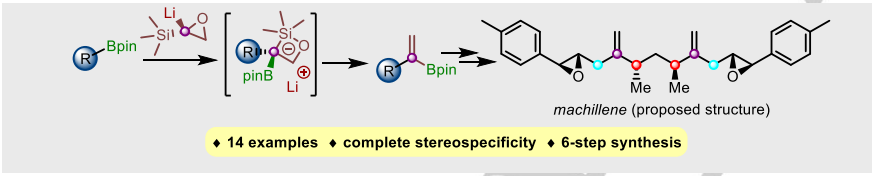

J. M. Fordham, M. N. Grayson V. K. Aggarwal**

Page No. – Page No.

Title

Vinylidene boronic esters can be obtained by the homologation of boronic esters with lithiated epoxysilane in a process where the selectivity for the vinyl boronic ester or vinyl silane product depends on the anion stabilizing ability of the R group. The methodology was applied in a short stereoselective synthesis of the proposed structure of machillene, however, synthetic and reported data did not match.